FDA Alert for Healthcare Professionals

Fluticasone propionate and salmeterol inhalation powder (marketed as Advair Diskus)

FDA ALERT [11/2005]: Long-acting beta$_2$-adrenergic agonists, such as salmeterol, an active ingredient in Advair Diskus, have been associated with an increased risk of severe asthma exacerbations and asthma-related death. FDA has requested that the package insert (labeling) for all long-acting beta$_2$-adrenergic agonists, including Advair Diskus, be revised to provide more information about this possible increased risk. FDA has also requested that a Medication Guide (FDA-approved patient information) containing information about these risks for patients and caregivers be dispensed with each prescription. FDA advises that, in the treatment of asthma, Advair Diskus should only be used in patients who have not adequately responded to other asthma controller medications, such as low-to-medium dose inhaled corticosteroids.

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of this drug, please contact the FDA MedWatch program at 1-800-FDA-1088 or http://www.fda.gov/medwatch/report/hcp.htm

Recommendations

Physicians with asthma patients using Advair Diskus, or who are considering prescribing the drug for asthma, should consider the following:

- Advair Diskus should not be the first medicine prescribed to treat a patient's asthma.
- Use Advair Diskus only for patients who have not responded to other asthma controller medications, such as inhaled corticosteroids. The National Heart, Lung, and Blood Institute (NHLBI) and World Health Organization (WHO) guidelines recommend inhaled corticosteroids as the first step in controller therapy, with long-acting beta$_2$-agonists as optional add-on therapy if low-to-medium dose inhaled corticosteroids do not adequately control the patient's asthma. Since Advair Diskus contains both a LABA and a corticosteroid, FDA therefore advises it only be started in asthma patients who have not responded adequately to low to medium dose inhaled corticosteroids without LABAs or in patients with asthma who are already taking both an inhaled corticosteroid and a LABA.
- Advise patients to seek medical treatment immediately if their asthma worsens.

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Data Summary

Data from a large placebo-controlled U.S. study [the Salmeterol Multi-center Asthma Research Trial (SMART)] that compared the safety of salmeterol or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). SMART was a randomized, double-blind study that enrolled long-acting beta$_2$-agonist–naive patients with asthma (average age of 39 years, 71% Caucasian, 18% African American, 8% Hispanic) to assess the safety of salmeterol (SEREVENT Inhalation Aerosol, 42 mcg twice daily over 28 weeks) compared to placebo when added to usual asthma therapy. A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355). The results of the interim analysis showed that patients receiving salmeterol may be at increased risk of fatal asthma events. In the total population, a higher rate of asthma-related deaths occurred in patients treated with salmeterol than in those treated with placebo (0.10% vs. 0.02%). These results led to the study being stopped prematurely.

Post-hoc subpopulation analyses were performed. In Caucasians, a higher rate of asthma-related deaths occurred in patients treated with salmeterol than in patients treated with placebo (0.07% vs. 0.01%). In African Americans, a higher rate of asthma-related deaths also occurred in patients treated with salmeterol compared to those treated with placebo (0.31% vs. 0.04%). Although the relative risks of asthma-related deaths were similar in Caucasians (5.82, 95% CI 0.70, 48.37) and African Americans (7.26, 95% CI 0.89, 58.94), estimates of excess deaths attributable to salmeterol are greater in African Americans. This observation is related to the fact that there was a higher rate of these events overall in the African American patients compared to Caucasian patients. The results of the SMART trial do not allow for conclusions about whether corticosteroids significantly change the asthma death risk profile of salmeterol or any LABA.

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Asthma-Related Deaths in the 28-week Salmeterol Multicenter Asthma Research Trial (SMART)

	Salmeterol n (%*)	Placebo n (%*)	Relative Risk† (95% Confidence Interval)	Excess Deaths per 10,000 patients‡ (95% Confidence Interval)
Total Population** Salmeterol: N=13176 Placebo: N=13179	**13 (0.10%)**	**3 (0.02%)**	**4.37 (1.25, 15.34)**	**8 (3, 13)**
Caucasian Salmeterol: N=9281 Placebo: N= 9361	**6 (0.07%)**	**1 (0.01%)**	**5.82 (0.70, 48.37)**	**6 (1, 10)**
African American Salmeterol: N=2366 Placebo: N=2319	**7 (0.31%)**	**1 (0.04%)**	**7.26 (0.89, 58.94)**	**27 (8, 46)**

* Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.

** The Total Population includes the following ethnic origins listed on the case report form: Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population includes those subjects whose ethnic origin was not reported. The results for Caucasian and African American subpopulations are shown above. No asthma related deaths occurred in the Hispanic (salmeterol n=996, placebo n=999), Asian (salmeterol n=173, placebo n=149), or "Other" (salmeterol n=230, placebo n=224) subpopulations. One asthma-related death occurred in the placebo group in the subpopulation whose ethnic origin was not reported (salmeterol n=130, placebo n=127).

† Relative risk is the ratio of the rate of asthma-related deaths in the salmeterol group to the rate in the placebo group. The relative risk indicates how much more likely an asthma-related death is in the salmeterol group than in the placebo group in a 28-week treatment period.

‡ Estimate of the number of additional asthma-related deaths due to salmeterol, assuming 10,000 patients were to receive salmeterol for a 28-week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related deaths multiplied by 10,000.

The results from SMART are similar to the results of another study, the Salmeterol Nationwide Surveillance (SNS) study, which was a 16-week clinical study performed in 25,180 patients with asthma in the United Kingdom in the early 1990s. The SNS study showed that the incidence of respiratory and asthma-related death was numerically, though not statistically, greater in patients treated with salmeterol (12 deaths out of 16,787 patients) versus albuterol (2 deaths out of 8,393 patients) added to usual asthma therapy.[1]

[1] Castle W, Fuller R, et al. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993; 306: 1034-7.